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(54) Title: METHOD FOR PREPARING HIGH PRESSURE/HIGH SHEAR DISPERSIONS CONTAINING PHYSIOLOGI-
CALLY ACTIVE INGREDIENTS

(57) Abstract: Disclosed are methods for preparing dispersions containing physiologically active or ingredients or aesthetic modi-
fiers, and optionally containing vehicles, including solvents. The dispersions are prepared using high pressure/high shear methods.

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**METHOD FOR PREPARING HIGH PRESSURE/HIGH SHEAR
DISPERSIONS CONTAINING PHYSIOLOGICALLY
ACTIVE INGREDIENTS**

5 Field of the Invention

The present invention relates to methods for preparing dispersions containing physiologically active ingredients.

Background of the Invention

10 Most topical preparations currently produced contain a wide variety of physiologically active ingredients and/or aesthetic modifiers. Physiologically active ingredients are compounds which cause a physical change to the body following their application. Examples of such ingredients include alpha hydroxy acids, antioxidants and vitamins. Aesthetic modifiers provide the composition with a defined physical
15 characteristic such as, for example, the degree of moisturization, oil content, and physical form of the composition.

Some examples of aesthetic modifiers include silicone fluids and derivatives, waxes, botanical (vegetable) oils, hydrocarbon-based oils, esters and fragrances. The performance of these ingredients is dependent upon the vehicle used to
20 deliver them. These vehicles range from simple solvents, such as water or ethanol, to complex emulsions.

Unfortunately not all active ingredients are completely soluble or compatible with all vehicles. For example, oil soluble active ingredients are typically not compatible with water or water-based gel vehicles. As a result, many products exhibit poor delivery of the
25 active ingredients, have poor tactile properties, or are thermodynamically unstable and result in a commercially unacceptable shelf life. Non-water based solvents can also be used as a vehicle for hydrophilic physiologically active materials or aesthetic modifiers. However, these preparations are typically not cosmetically elegant. Further, these non-water based solvents can cause unwanted side effects such as irritation or damage to the
30 epithelial surface to which they are applied.

5 High pressure high shear dispersions are finding increasing application in cosmetic, personal care, over-the-counter (OTC), Rx, nutritional and food products. These systems can be mixed into a compatible base to create products with superior performance and aesthetic properties.

 Generally, a dispersion is formed by dispersing a hydrophobic phase into a
10 polar, hydrophilic phase, which is principally water. However, if the material to be dispersed has too much polarity, or if it is solid in its native state it will not disperse readily and therefore is excluded from use in developing new treatment products. This situation is unfortunate and does not allow for the preparation of physiologically efficacious products using materials that can treat a particular disorder but which are not
15 water dispersible in their own right.

 Many physiologically active agents are unable to disperse directly into an aqueous phase. These materials usually are simply dissolved into solvents before they are applied to the surface to be treated. These solvent systems are usually hydrocarbon based materials of varying polarity. The solvent is selected based on its ability to dissolve the
20 physiologically active material of choice to treat a particular topical disorder. These solvent systems often are irritating, can damage the surface to which they are applied and are very unaesthetic. Further, if the physiologically active material is unstable to conventional processing methods, an alternative method of introducing the material into a product is necessary to maintain its beneficial properties.

25 To overcome the negative properties usually associated with the use of simple aqueous or non-water based solvents, a formulator typically uses stable dispersions to deliver the physiologically active ingredient or aesthetic modifier to the epithelial surface to be treated. These dispersions form either spherical micelles of one or more hydrophobic liquid materials in water or spherical droplets of water in a hydrophobic
30 fluid. Such dispersions are typically prepared by creating the oil phase and water phase then mixing the two phases together.

 Specifically, the hydrophobic physiologically active ingredients or aesthetic modifiers are dissolved in a suitable oil phase and the hydrophilic physiologically active ingredients or aesthetic modifiers are dissolved in water, and then the two phases are
35 combined with one or more emulsifying agents which are incorporated into either or both the water and oil phases. These emulsifiers are surface active agents (surfactants) whose role is to reduce the surface tension between the oil and water phases thereby making the

5 combination of the two phases more stable. Such "emulsions" are generally prepared by heating the oil and water phases to elevated temperatures exceeding 70-75°C before combining, then slowly cooling the combined phases to ensure the development of the suitable crystalline and liquid crystalline structures which gives the emulsion its characteristic properties. These emulsions usually have a homogeneous opaque white
10 appearance and a smooth or pleasant feeling upon application to the skin or other epithelial surface. However, the use of typical emulsion products to deliver physiological or aesthetic benefits has many limitations.

The presence of significant amounts of surfactant can strip material from the lipid barrier of the skin or the lipid bilayer of epithelial cell membranes leaving the
15 tissue vulnerable. Thus, the surfactants themselves can evoke an irritation or the damaged barrier will permit the passage of other materials that can cause irritation or increase skin sensitivity and allergic reactions. The literature is replete with clinical evidence of the damaging consequences that can occur with the use or overuse of surfactants. For example, Effendy I, Maibach HI, "Surfactants and experimental irritant contact
20 dermatitis", *Contact Dermatitis* 1995 Oct; 33(4):217-25 indicates that "[m]any surfactants elicit irritant reactions when applied to the skin, partially due to their relative ability to solubilize lipid membranes."; Barany E, Lindberg M, Loden M, "Biophysical characterization of skin damage and recovery after exposure to different surfactants", *Contact Dermatitis* 1999 Feb;40(2):98-103, states that "[t]he majority of adverse skin
25 reactions to personal-care products are presumed to be caused by irritant substances, like surfactants."

Moreover, there are limitations to conventional topical formulations. For example, many materials with interesting aesthetic properties are not easily produced in an emulsion such as, for example, fluorinated compounds. Additionally, each time the oil or
30 water phase is changed, the emulsifiers would need to be rebalanced. The incorporation of additional materials using conventional techniques can affect surface tension adversely, leading to the final product becoming unstable.

Many topical products formulated contain active ingredients and/or certain aesthetic modifiers which readily become destabilized in emulsions, causing them to
35 degenerate or deteriorate. For example, prolonged heating of the water and oil phases can thermodynamically modify the active molecule or can kinetically accelerate the reaction of the active with another agent in the emulsion or with air if the material is oxygen sensitive.

5 Moreover, lowering the surface tension of a topical composition generally increases the surface exposure of the active or sensitive aesthetic modifier to oxygen and other destabilizing materials. For example, when retinol is the active ingredient, the instability of the composition leads to lower efficacy. The instability of an unsaturated fatty acid as an aesthetic modifier leads to color changes and malodors in the composition. Since the
10 time between manufacturing and sale of a cosmetic product is typically several weeks, the product is often no longer "fresh" or effective since the active ingredient has degenerated or deteriorated. To offset instability problems, many other materials such as chelating agents, antioxidants and masking agents are usually included in the formulation.

Typical emulsions are time consuming to prepare, require heating, are
15 produced in multiple phases, are slow cooling, and often require high shear conditions to get the particle size small enough for maximum stability. Larger batches may take from 8 to 24 hours to process and can take several days to set up. It is also very difficult to get excellent reproducibility of an emulsion. If any factors such as the heating, cooling or mixing rates are not carefully duplicated, the preparation may have different properties
20 than the preceding batches of the same product. Often the difference of a single parameter is significant enough to cause the product to be outside the established optimum specifications. These batches then have to be either discarded or re-worked.

The lack of reproducibility is especially problematic when the product contains a drug or other physiologically active ingredient. Lack of reproducibility can
25 effect product performance and end user satisfaction. The lack of reproducibility will result in products from different batches having different aesthetic properties which the end user will perceive as a lack of quality and will ultimately lead to consumer dissatisfaction or reduced compliance.

Standard emulsion preparations also have a high cost to manufacture. This
30 is due to a variety of factors including the energy to heat the batch, the specialized equipment required to process the emulsion such as specialized pumps and cooling/heating equipment and the length of process ties up equipment and personnel, resulting in increased overhead and lost opportunity time.

Applicants have now discovered a method of forming stable dispersions of
35 physiologically active agents, comprising dispersing a hydrophobic phase into a polar hydrophilic phase which is principally water. The hydrophobic phase, which is nonpolar

- 5 or low polar, is combined with the aqueous phase using high pressure high shear conditions to create a stable dispersion.

Objects of the Invention

- Applicants have discovered a method of making more efficacious
10 formulations than those obtained by prior art methods.

Applicants have discovered a method of forming compositions having greater ingredient stability than prior art compositions.

Applicants have discovered a method of forming compositions which are more cosmetically elegant and less irritating than prior art formulations.

- 15 The method of the invention also provides greater flexibility in obtaining formulations, and substituting ingredients, and allows the formulator to disregard HLB rebalancing which is often a problem with the changes to formulations in the prior art. The method of the invention permits easier scale up to manufacturing.

- The method of the invention involves reduced manufacturing costs by
20 reducing processing time and energy costs and lower capital investment in equipment.

The method of the invention results in much more consistent reproducibility than prior art methods, causing less wasted batches and work-off.

Summary of the Invention

- In one embodiment, the invention is directed to methods of forming a dispersion of a nonpolar or slightly polar physiologically active agent in a composition.
25 The method of the invention includes the steps of mixing a nonpolar or slightly polar physiologically active agent with a solvent or cosolvent, and subjecting it to high pressure/high shear mixing to form a stable dispersion in water, with a particle size of from about 50 to about 1000 nm. In other embodiments, the dispersion may have a particle size of from about 50 to about 500 nm.

30

Detailed Description of the Invention

- A hydrophobic active ingredient or hydrophobic adjuvant of the present invention is an active ingredient or adjuvant which has a non polar property which makes it essentially insoluble in water or water and polar solvent solutions. Hydrophobic active
35 ingredients of the present invention include, but are not limited to, partially and fully hydrophobic active ingredients. For example, hydrophobic active ingredients encompassed

- 5 by the present invention include compounds and complexes which contain a hydrophobic moiety.

The topical preparation of the present invention may also include non-hydrophobic active ingredients and non-hydrophobic adjuvants.

- Suitable active agents include, but are not limited to, anti-acne agents, antimicrobial agents, antiinflammatory agents, analgesics, anti-itch agents, antipruritic agents, antiedema agents, antipsoriatic agents, antifungal agents, skin protectants, sunscreen agents, vitamins, antioxidants, scavengers, antiirritants, antibacterial agents, antiviral agents, antiaging agents, photoprotection agents, hair growth enhancers, hair growth inhibitors, hair removal agents, antidandruff agents, anti-seborrheic agents, exfoliating agents, wound healing agents, anti-ectoparasitic agents, sebum modulators, immunomodulators, hormones, botanicals, moisturizers, astringents, sensates, antibiotics, anesthetics, steroids, tissue healing substances, tissue regenerating substances, amino acids, peptides, minerals, ceramides, biohyaluronic acids, and any combination of any of the foregoing.

- Preferred anti-acne agents include, but are not limited to, salicylic acid, retinoic acid, alpha hydroxy acid, benzyl peroxide, sodium sulfacetamide, clindamycin, and any combination of any of the foregoing. Preferred combinations of anti-acne agents to be incorporated in the composition include salicylic acid, retinoic acid, and hydrocortisone; sodium sulfacetamide and clindamycin; salicylic acid and clindamycin; salicylic acid, alpha hydroxy acid, and tetrahydrozoline.

- Suitable antimicrobial agents include, but are not limited to, Benzalkonium chloride, Benzethonium chloride, Chlorhexidine gluconate, Chloroxylenol, Clindamycin, Cloflucarban, erythromycin, Fluorosalan, Hexachlorophene, Hexylresorcinol, Iodine complex, Iodine tincture, Para-chloromercuriphenol, Phenylmercuric nitrate, Thimerosal, Vitromersol, Zyloxin, Triclocarban, Triclosan, Methyl-benzethonium chloride, Nonyl phenoxypoly (ethyleneoxy) ethanol-iodine, Para-chloro-meta-xyleneol, Providone-iodine complex, Poloxamer-iodine complex, Triclorcarban, Undecylium chloride-iodine complex, and any combination of any of the foregoing.

- Suitable antiinflammatory agents include, but are not limited to, Alidoxa, Allantoin, Aloe Vera, Aluminum acetate, Aluminum hydroxide, Bismuth subnitrate, Boric acid, Calamine, Casein, Cellulose, microporous, Cholecalciferol, Cocoa butter, Cod liver oil, Colloidal oatmeal, Cystein hydrochloride, Dexpanthenol, Dimethicone, Glycerin,

- 5 Kaolin, Lanolin, Live yeast cell derivative, Mineral oil, Peruvian balsam, Petrolatum, Protein hydrolysate, Racemethionine, Shark liver oil, Sodium bicarbonate, Sulfur, Talc, Tannic acid, Topical starch, Vitamin A, Vitamin E, White petrolatum, Zinc acetate, Zinc carbonate, Zinc oxide, Hydrocortisone, Betamethasone, Ibuprofen, Indomethicin, Acetyl salicylic acid, Tacrolimus, Fluocinolone acetonide, Sodium sulfacetamide, and any
10 combination of any of the foregoing.

The compositions of the invention may include a wide range of active agents having various anti-irritation and anti-inflammatory activities. Suitable physiologically active agents which are too polar to be effectively dispersed in an aqueous (or hydrophilic) phase are the following:

15

Sansurf® Shea butter, Sansurf® DMG and Dermaguard, which have desirable barrier properties;

- Silox chamomile, sea salt, A/I liposomes, sea parsley, Sansurf® Shea Butter, InCyte® Lemon Peel, Melarrest™ L, and Bisabolol SS, which act to block signal
20 development;

ExCyte® Hops and Melarrest™ L, which block recruitment;

ExCyte® Hops, sea parsley and Heather ExCyte®, which act as MMP suppression and block neutralization agents;

- MPC, Sansurf® BFA, Sansurf® oils, ceramides, sphingolipids and
25 liposomes, which act as barrier repairs;

Hyaluronic acid quaternary compounds, MCP, HA-SOL, AMC, Seamollient®, Botanigels, Categel, moisturizations liposomes, and humectant liposomes, which act as humectants;

- MPC, Moistureguard, vegepure, Sansurf® oils and polyfix, which act as
30 occlusive barrier agents;

Solarease™ OMC/1789, Solarcat™ OMC/1789 and TioSperse™ Ultra, which act as UV absorbers;

A/O complex, silox GT, lemon balm, ExCyte® green tea, PhoCyte® lemon peel, InCyte® apple and InCyte® kola, which act as anti-oxidants; and

- 35 beta glucan, which enhances the immune system (acts as an immune stimulator and enhancement).

5 Suitable analgesics include, but are not limited to, diphenhydramine, tripeleminamine, benzocaine, dibucaine, lidocaine, tetracaine, camphor, menthol, phenol, resorcinol, m-cresol, juniper tar, methylsalicylate, turpentine oil, capsaicin, methyl nicotinate, beta-glucan, and any combination of any of the foregoing.

 Suitable antierythematous agents include, but are not limited to, tetrahydrozoline
10 and hydrocortisone.

 Suitable antipruritic agents include, but are not limited to, benadryl, pramoxine, antihistamines, and any combination of any of the foregoing.

 Suitable antiedematous agents include, but are not limited to, pregnenolone acetate, tannin glycosides, and any combination of any of the foregoing.

15 Suitable antipsoriatic agents include, but are not limited to, calcipotriene, coal tar, anthralin, vitamin A, and any combination of any of the foregoing. Preferred combinations of antipsoriatic agents include, but are not limited to, hydrocortisone, retinoic acid, and alpha hydroxy acid; doxonex, salicylic acid, and a sunscreen agent; indomethacin, salicylic acid, and urea; anthralin and salicylic acid; and anthralin and
20 indomethacin. Other suitable antipsoriatic agents include, but are not limited to, calcipotriene, coal tar, anthralin, vitamin A, and any combination of any of the foregoing.

 Suitable antifungal agents include, but are not limited to, clioquinol, haloprogin, miconazole nitrate, clotrimazole, metronidazole, tolnaftate, undecylenic acid, iodoquinol, and any combination of any of the foregoing.

25 Suitable skin protectants include, but are not limited to, cocoa butter, dimethicone, petrolatum, white petrolatum, glycerin, shark liver oil, allantoin, and any combination of any of the foregoing.

 Suitable sunscreen agents include, but are not limited to, octyl methoxycinnamate, avobenzone, benzophenone-3, octacrylene, titanium dioxide, zinc
30 oxide, and any combination of any of the foregoing.

 A preferred sunscreen agent is a mixture of octylmethoxycinnamate, butyl methoxydibenzoylmethane, cyclomethicone, one or more phospholipids and water, and is available as SolareaseTM from Collaborative Laboratories, Inc. of Stony Brook, New York.

 Suitable antioxidants include, but are not limited to, scavengers for lipid
35 free radicals and peroxy radicals, quenching agents, and any combination of any of the foregoing.

5 Suitable antioxidants include, but are not limited to, tocopherol, BHT, beta carotene, vitamin A, ascorbic acid, ubiquinol, ferulic acid, azelaic acid, thymol, catechin, sinapic acid, EDTA, lactoferrin, rosmariquinone, hydroxytyrosole, sesamol, 2-thioxanthine, nausin, malvin, carvacone, chalcones, glutathione isopropyl ester, xanthine, melanin, guanisone, lophophyrins, 8-hydroxyxanthine, 2-thioxanthione, vitamin B₁₂,
10 plant alkaloids, catalase, quercetin, tyrosine, SOD, cysteine, methionine, genistein, NDGA, procyanidin, hamamelitannin, ubiquinone, trolox, licorice extract, propyl gallate, sinapic acid, and any combination of any of the foregoing.

 Suitable vitamins include, but are not limited to, vitamin E, vitamin A palmitate, vitamin D, vitamin F, vitamin B₆, vitamin B₃, vitamin B₁₂, vitamin C, ascorbyl
15 palmitate, vitamin E acetate, biotin, niacin, DL-panthenol, and any combination of any of the foregoing.

 Suitable amino acids include, but are not limited to, glycine, serine, and any combination of any of the foregoing.

 Suitable adjuvants include, but are not limited to, aesthetic modifying
20 agents. The composition of the current invention includes at least one or more aesthetic modifying agents. An aesthetic modifying agent is a material which imports desirable tactile, olfactory, taste or visual properties to the surface to which it is applied. These materials can either be hydrophobic or hydrophillic. The aesthetic modifier generally is a hydrophobe. Preferably the hydrophobe is oil, wax, solid or paste. The hydrophobic
25 aesthetic modifiers which are used in the present invention are dispersed into an aqueous phase typically by ultra high shear mixing, microfluidization or any other method known in the art which can produce a commercially stable dispersion that is essentially free of emulsifying surface active agents. The dispersions of the present invention are produced by mixing from about 0.1% to about 70% hydrophobic aesthetic modifying agents or
30 blends of aesthetic modifying agents with from about 30% to about 99.9% aqueous phase employing high pressure/high shear conditions. This produces a homogenous fluid dispersion which is stable for a commercially relevant period of time. The preferred pressure for preparing the dispersion is between about 9,000 to about 25,000 psi with a desired shear that creates an average particle size of between about 50 to about 1000
35 nanometers.

5 **Exemplary Embodiments of the Invention**

Example 1: Essential Fatty Acid ("EFA") Complex

 A first composition was formed in two beakers. The wgt % values are calculated based on the wgt % of the resulting final composition, after the compositions of the beakers are combined.

10 In a first beaker was mixed 10 wgt % Emersol® 221 oleic acid, manufactured by Henkel Chemical Co.; 15 wgt % Emersol® 315 linoleic acid, manufactured by Henkel Chemical Co.; 5 wgt % industrene 120 liquid, linolenic acid enriched in coconut oil manufactured by CK Witco Chemical Co.; 0.05 wgt % ceramide III; 0.0001 wgt % phytospergine, manufactured by Doosan Chemical Co.; and 0.05 wgt
15 % cholesterol. The composition is heated to 80°C in a water bath and stirred until clear.

 In a second beaker was mixed 54.3999 wgt % Dow Corning 345 fluid, a cyclomethicone; 10.00 wgt% Vitamin E; 5.00 wgt % alcolec BS, a lipid supplied by American Lecithin; and 0.50 wgt % liquapar PE, a mixture of phenoxyethanol, isopropylparaben and butylparaben, sold by Sutton. The composition was mixed until
20 uniform at room temperature.

 The first beaker was removed from heat and the contents of the first beaker were added to the second beaker. The second beaker was cooled to room temperature. The composition was then filtered through Whatman 1 paper.

 The resulting composition was homogeneous.

25

Example 2: Sansur® EFA Composition

 A composition was formed in two beakers. The wgt % values were calculated based on the basis of the wgt % of the resulting composition, after the two beakers were combined.

30 In a first beaker, 60.95 wgt% distilled water; 25.00 wgt% of the EFA complex of Example 1; 10.0 weight% soybean oil; and 1.80 wgt% of Germazide MPB, were mixed.

 In a second beaker, 0.25 wgt % Phosphlipon 90H (sold by American Lecithin Co.); and 2.00 wgt% basis LP 20H are mixed.

35 The contents of the second beaker were added to the first beaker, and the resulting composition was subjected to mixing with a Silverson high shear mixer until it

- 5 was homogeneous, and was then processed through a M110 Microfluidiser, manufactured by Microfluidics, Inc. of Massachusetts, at from 9,000-25,000 psi.

Example 3: SolarCat™ Composition

- 10 A first composition was formed in three beakers. The wgt % values were calculated based on the wgt % of the resulting final composition, after the compositions of the beakers are combined.

In a first beaker was mixed 25 wgt % Escalol 587, manufactured by Henkel Chemical Co.; 3.0 wgt % Escalol 567, manufactured by Henkel Chemical Co. The composition was heated to 75°C and stirred until clear.

- 15 In a second beaker was mixed 67.5 wgt % distilled water; 2.0 wgt % Germazide® MPB.

- In a third beaker was mixed 2.5 wgt % Catemol S-180S, manufactured by Phoenix Chemical. The compositions in the second and third beaker were mixed at 75°C. The contents of the second beaker and third beaker were added to the first beaker, and the
20 resulting composition was then processed through a M110 Microfluidizer, manufactured by Microfluidics, Inc. of Massachusetts, at from 9,000-25,000 psi.

Example 4: Solarease® OS/B3 Composition

- 25 A first composition was formed in three beakers. The wgt % values are calculated based on the wgt % of the resulting final composition, after the compositions of the beakers are combined.

In a first beaker was mixed 25 wgt % Escalol 587, manufactured by Henkel Chemical Co.; 3 wgt % Benzophenone-3, manufactured by ISP Van Dyke. The composition was heated to approximately 80°C and stirred until clear.

- 30 In a second beaker was mixed 67.5 wgt % distilled water; 2.0 wgt % Germazide® MPB.

- In a third beaker was mixed 2.5 wgt % Basis LP-20H, manufactured by Ikeda; 0.5 wgt % Phospholipon 80H manufactured by American Lecithin. The composition in the second beaker was subjected to mixing with a Silverson high shear
35 mixer while slowly adding the composition of third beaker until it was homogeneous. The contents of the second beaker and third beaker were added to the first beaker, and the

- 5 resulting composition was then processed through a M110 Microfluidizer, manufactured by Microfluidics, Inc. of Massachusetts, at from 9,000-25,000 psi.

Example 5: Solarease® II Composition

- A first composition was formed in five beakers. The wgt % values are
10 calculated based on the wgt % of the resulting final composition, after the compositions of the beakers are combined.

- In a first beaker was mixed 37.5 wgt % Escalol 557, manufactured by Henkel Chemical Co.; 10 wgt % Parsol 1789; 1.8 wgt % Silicone Based Lemon Balm Extract. The composition was heated to approximately 75°C and stirred until dissolved.
15 The composition was then cooled to approximately 25°C.

In a second beaker was mixed 0.1 wgt % Disodium EDTA, manufactured by Spectrum; 0.4 wgt % Potassium Sorbate USP/NF, manufactured by Tri-K; 0.01 wgt % Phytic Acid manufactured by Sigma and 46.39 wgt % distilled water. The composition was then mixed in a separate vessel until all is dissolved.

- 20 In a third beaker was added 1.85 wgt % Germazide® MPB. The composition of the second and third beaker were mixed until homogenous.

In a fourth beaker was added 0.2 wgt % 99% TEA manufactured by Kramer Chemical. The pH of this composition was then adjusted to approximately 6.50.

- In a fifth beaker was mixed 1.5 wgt % of Basis LP-20H manufactured by Ikeda and 0.25 wgt % Phospholipon 80H manufactured by American Lecithin.
25

- The composition in the second beaker, third beaker and fourth beaker was subjected to mixing with a Silverson high shear mixer while slowly adding the composition of the fifth beaker until it was homogeneous. The contents of the first beaker was then added with the continuation of the mixing with a Silverson high shear mixer. The
30 entire composition was then processed through a M110 Microfluidizer, manufactured by Microfluidics, Inc. of Massachusetts, at from 9,000-25,000 psi.

Example 6: Sansurf® OMC Composition

- A first composition was formed in one beaker. The wgt % values are
35 calculated based on the wgt % of the resulting final composition, after the compositions of the beakers are combined.

5 In a beaker was mixed 45.90 wgt % distilled water; 28.57 wgt % Uvinul N-539-SG, manufactured by BASF; 21.53 wgt % Escalol 557 manufactured by Henkel Chemical Co.; 1.85 wgt % Germazide® MPB; 2.00 wgt % Basis LP-20H manufactured by Ikeda and .25 wgt % Phospholipon 80H manufactured by American Lecithin. The composition was subjected to mixing with a Silverson high shear mixer until it was
10 homogeneous. The entire composition was then processed through a M110 Microfluidizer, manufactured by Microfluidics, Inc. of Massachusetts, at from 9,000-25,000 psi.

Example 7: Sansurf® SPF-30

A first composition was formed in three beakers. The wgt % values are
15 calculated based on the wgt % of the resulting final composition, after the compositions of the beakers are combined.

In a first beaker was mixed 25.0 wgt % Escalol 557, manufactured by Henkel Chemical Co.; 8.0 wgt % Escalol 567, manufactured by Henkel Chemical Co.; 6.0 wgt % Parsol 1789; and 12.5 wgt % Crodamol ISNP manufactured by Croda. The
20 composition was heated to approximately 75°C and stirred until dissolved. The composition was then cooled to room temperature.

In a second beaker was mixed 44.0 wgt % distilled water; 2.0 wgt % Germazide® MPB; 0.25 wgt % Potassium Sorbate manufactured by Tri-K.

In a third beaker was mixed 2.0 wgt % Basis LP-20H manufactured by
25 Ikeda and 0.25 wgt % Phospholipon 80H manufactured by American Lecithin. The composition of the second and third beaker was subjected to mixing with a Silverson high shear mixer while slowly adding the composition of the first beaker until it was homogeneous. The entire composition was then processed through a M110 Microfluidizer, manufactured by Microfluidics, Inc. of Massachusetts, at from 9,000-25,000 psi.

30 The various commercially available products used in the exemplary embodiments and elsewhere in the application are described further below:

Germazide® MPB is a mixture of phenoxyethanol, chlorphenesin, glycerin, methylparaben, and benzoic acid and is available from Collaborative Laboratories, Inc. of East Setauket, NY.

35 Solarease® is a mixture of octylmethoxycinnamate, butyl methoxydibenzoylmethane, cyclomethicone, phospholipids, and water and is available from Collaborative Laboratories, Inc. of East Setauket, NY.

5 Seamollient® is a mixture of water, algae extract, chlorphenesin, propylene glycol, sodium dehydroacetate, and phenoxyethanol and is available from Collaborative Laboratories, Inc. of East Setauket, NY.

 Sansurf® Cyclomethicone is a mixture of water, cyclopentasiloxane and phospholipids and is available from Collaborative Laboratories, Inc. of East Setauket, NY.

10 Solarease II is a mixture of octylmethoxycinnamate, butyl methoxydibenzoylmethane, cyclomethicone, phospholipids, and water and is available from Collaborative Laboratories, Inc. of East Setauket, NY.

 Vitamin A & E liposomes is a mixture of water, phospholipids, tocopheryl acetate, and retinyl palmitate and is available from Collaborative Laboratories, Inc. of
15 East Setauket, NY.

 Sansurf® DMG is a mixture of water, petrolatum, dimethicone, perfluoropolymethylisopropylether, stearamidopropyl dimethylamine, stearic acid, and tocopherol acetate, and is available from Collaborative Laboratories, Inc. of East Setauket, NY.

20 Solarcat™ is a mixture of water, octyl methoxycinnamate, butyl methoxydibenzoylmethane, cyclomethicone, stearamidopropyl dimethylamine, stearamidopropyl dimethylamine stearate, and balm mint extract and is available from Collaborative Laboratories, Inc. of East Setauket, NY.

 Catezomes™ OMC is a mixture of octyl methoxycinnamate and
25 stearamidopropyl dimethylamine stearate and is available from Collaborative Laboratories, Inc. of East Setauket, NY.

 Parsol 1789 is a butyl methoxydibenzoylmethane sold by Givaudan-Roure Specialty Division.

30 **Example 8: In-Vitro Sun Protection Factor ("SPF") Protocol**

Background:

 The SPF 290 is composed of an ultraviolet source, monochromator and a detector. The source is a 125 W xenon lamp that emits ultraviolet (UVB) and near ultraviolet (UVA) radiation. This radiation then is filtered and attenuated to
35 accurately simulate a solar irradiance spectrum. The radiation passes through the sample where a portion of it is adsorbed. The light not adsorbed enters the integrating sphere, where it is collected and then enters the monochromator. The

- 5 monochromator separates the light into discrete wavelength bands, which are picked up by the detector.

The SPF 290 feeds this information into a data acquisition card, which plugs into a computer. The computer uses this feedback to calculate SPF values for the sample. SPF is calculated using a series of equations. First, the monochromatic
 10 protection factor (MPF) is calculated as the reciprocal of transmittance. $MPF = 1/T$. Transmittance in turn is the voltage feedback from the sample scan divided by the feedback from the reference scan. $T = S/R$. The value for sun protection factor is given by the equation

$$SPF = \sum E \cdot B / E \cdot B / MPF$$

- 15 where E is the spectral irradiance of sunlight and B is the erythral effectiveness. The software can calculate the standard deviation and mean of a series of MPF and SPF calculations.

Sample Preparation:

- 20 Cut a 5 cm x 7.5 cm piece of Transpore tape (3M Inc.) and place it on a glass slide using double sided tape (rough surface facing up). The sunscreen-containing agent is distributed across the rough surface of the Transpore tape evenly at a density of 2 $\mu\text{g}/\text{cm}^2$. The only way to apply the agent is to pipette it in 10 μl evenly spaced drops on the substrate. Once the sunscreen has been applied to the substrate, the material is rubbed into
 25 the tape with a gloved finger. The rubbing action should mimic the rubbing action on human skin in-vivo. Start a timer upon completion of the product rub in. Allow the substrate to sit for 20 minutes (dry down time).

The following table shows a product which can be formulated to make an SPF product.

30

Product	Percentage Used	In-Vitro SPF
Sansurf OMC B-3	25	23.92
Sansurf OMC B-3 1789	30	43.06
Solarease II	20	22.1

35

5 All patents, publications, applications, and test methods mentioned herein are hereby incorporated by reference. Many variations of the present invention will suggest themselves to those skilled in the art in light of the above, detailed description. All such obvious variations are within the full intended scope of the appended claims.

What is claimed is:

- 1 1. A method of forming a dispersion of a nonpolar or slightly polar
2 physiologically active agent in a composition comprising water, said method comprising
3 the steps of
4 mixing said nonpolar or slightly polar physiologically active agent with a
5 solvent or cosolvent;
6 subjecting said mixture of said nonpolar or slightly polar physiologically
7 active agent with said solvent to high pressure/high shear mixing to form a stable high
8 pressure/high shear dispersion in water, with a particle size of from about 50 to about 1000
9 nm.
- 1 2. The method of claim 1 wherein said physiologically active agent is selected
2 from the group consisting of retinol, butyl methoxydibenzoylmethane, benzophenone-3 or
3 ceramides.
- 1 3. The method of claim 1 wherein said solvent or cosolvent is selected from
2 the group consisting or cosolvent is selected from the group consisting of soybean oil,
3 octylmethoxycinnamate, octyl salicylate and cyclomethicone.
- 1 4. The method of claim 1 wherein said physiologically active agent is retinol
2 and said solvent or cosolvent is soybean oil.
- 1 5. The method of claim 1 wherein said physiologically active agent is butyl
2 methoxydibenzoylmethane and said solvent or cosolvent is octylmethoxycinnamate.
- 1 6. The method of claim 1 wherein said physiologically active agent is
2 benzophenone -3 and said solvent or cosolvent is octyl salicylate.
- 1 7. The method of claim 1 wherein said physiologically active agent is
2 ceramide and said solvent or cosolvent is cyclomethicone.

1 8. The method of claim 1, wherein said physiologically active agent does not
2 form a stable dispersion with said aqueous composition in the absence of said high
3 pressure/high shear mixing.

1 9. The method of claim 5 wherein said butyl methoxydibenzoylmethane is
2 parsol 1789.

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(54) Title: METHOD FOR PREPARING HIGH PRESSURE/HIGH SHEAR DISPERSIONS CONTAINING PHYSIOLOGICALLY ACTIVE INGREDIENTS

(57) Abstract: Disclosed are methods for preparing dispersions containing physiologically active or ingredients or aesthetic modifiers, and optionally containing vehicles, including solvents. The dispersions are prepared using high pressure/high shear methods.

INTERNATIONAL SEARCH REPORT

International Application No

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A. CLASSIFICATION OF SUBJECT MATTER

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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, PAJ, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 98 14174 A (VIVORX PHARMACEUTICALS, INC. ET AL.) 9 April 1998 (1998-04-09) page 10, line 12 - line 20 page 14, line 11 - line 21 page 15, line 18 - line 20 page 17, line 19 - line 21 page 18, line 6 - line 19 ---	1,3
X	US 6 004 566 A (FRIEDMAN ET AL.) 21 December 1999 (1999-12-21) column 3, line 26 - line 33 column 3, line 59 - line 64 example 1 ---	1
A	WO 99 26599 A (SCHERING-PLOUGH HEALTHCARE PRODUCTS, INC. ET AL.) 3 June 1999 (1999-06-03) example 1 -----	2,3

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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